National Institute of Allergy and Infectious Diseases
National Institutes of Health

Revised April 11, 2005

Questions and Answers

Leadership for HIV/AIDS Clinical Trials Networks

Overview

1. What is the purpose of the Request for Applications for Leadership for HIV/AIDS Clinical Trials Networks?

This Request for Applications (RFA) is the first of two RFAs that together will restructure the HIV/AIDS clinical trial networks supported by the National Institute of Allergy and Infectious Diseases (NIAID). The Division of AIDS (DAIDS), a component of NIAID, currently funds seven clinical trials networks encompassing HIV/AIDS prevention, vaccine and therapeutic research. Through their multicenter clinical trials research, these networks have made enormous strides in advancing science and the clinical care of HIV-infected individuals: they have provided the scientific alliances and infrastructure that led to the discovery of antiretrovirals to treat HIV-1 infection in adults and children; strategies to successfully prevent mother-to-child HIV transmission; and significant progress in the global search for an AIDS vaccine. To build on these successes and to prepare for continuing research challenges worldwide, this competition is designed to improve the coordination, collaboration, efficiency and flexibility of the research networks and focus research efforts on six areas of highest priority

- Vaccine research and development
- Translational research/drug development
- Optimization of clinical management, including co-morbidities
- Microbicides
- Prevention of mother-to-child transmission (MTCT) of HIV
- Prevention of HIV infection

The specific structure and management of the newly funded clinical research networks will enable DAIDS to

- Maximize scientific opportunities by integrating and coordinating HIV/AIDS prevention, vaccine and therapeutic research while maintaining a flexible and responsive approach to emerging research challenges
- Build and strengthen HIV/AIDS research capacity, especially in resource-limited settings
- Improve research efficiency through the shared use of key support services
- Improve evaluation methods to ensure that the highest priorities are addressed

2. Why is it necessary to restructure the existing clinical trials Networks?

This RFA will allow for the continued evolution of NIAID's clinical research effort. The competition process will create a new structure that will more closely integrate prevention, vaccine and therapeutic research, particularly in resource-limited settings; increase efficiency and maximize the use of limited resources; foster collaboration among the various entities conducting HIV/AIDS research; and, most importantly, ensure that the most critical research priorities and scientific questions are addressed.

3. What led to the restructuring effort?

DAIDS established its first HIV therapeutic clinical research network (the AIDS Clinical Trials Group) in 1987 to develop an infrastructure that could rapidly address critical scientific questions about how to treat HIV infection and associated complications. Additional networks were subsequently established to address other specific areas of research, such as vaccines and non-vaccine prevention research. Together, these networks provided the basis for much of what is known about HIV/AIDS today and laid the foundation for future research activities.

As the networks advanced the field of HIV/AIDS research, they also continued to evolve to more effectively respond to the changing course of the epidemic, the evolving demographics of AIDS and changing research needs. For example, the AIDS Clinical Trials Group evolved into the Adult AIDS Clinical Trials Group and the Pediatric AIDS Clinical Trials Group, in order to focus research efforts on HIV-infected infants and children and strategies for preventing MTCT. The AIDS Vaccine Evaluation Group and the HIV Network for Prevention Trials evolved into the HIV Vaccine Trials Network and the HIV Prevention Trials Network, in order to more effectively focus vaccine and prevention research capabilities and enhance global research capacity.

Each of these research networks has made critical contributions to the fight against HIV/AIDS, providing a wealth of information on preventing HIV transmission and improving the care and treatment of HIV-infected individuals around the world. It became clear, however, through several years of consultation with researchers, clinicians, community, nurses, advocates and people living with and at risk of HIV/AIDS that, given the ever-changing face of the epidemic and evolving scientific challenges, the network structure for conducting HIV/AIDS clinical research also needed to evolve in order to address global research needs.

4. What is unique about this RFA?

Previous competitions focused on specific areas of scientific focus (e.g., therapeutics, prevention vaccines). This is the first time that applications are being solicited to encompass a broad spectrum of NIAID-supported HIV/AIDS multicenter clinical trials research in prioritized areas of research.

By competing a diverse portfolio of multicenter clinical trials research at the same time, NIAID seeks to

- Establish priorities across a broad range of clinical research areas and activities
- Coordinate research activities across a consortium of linked networks
- Increase efficiency through resource sharing
- Flexibly allocate and distribute resources in response to priority research opportunities

- Leverage complementary strengths and resources within and outside the networks

It is also anticipated that the new research structure outlined in the RFA will encourage applications from qualified organizations that have not previously participated in NIAID-supported research, bringing new partners to NIAID's HIV/AIDS clinical trials research effort.

This RFA represents a collaboration of resources and scientific expertise between NIAID and other NIH Institutes and Centers (IC) that support HIV/AIDS-related research, including the Fogarty International Center (FIC); National Cancer Institute (NCI); National Institute of Child Health and Human Development (NICHD); National Institute of Dental and Craniofacial Research (NIDCR); National Institute of Mental Health (NIMH); National Institute on Alcohol Abuse and Alcoholism (NIAAA); and National Institute on Drug Abuse (NIDA). The Office of AIDS Research (OAR) at NIH, which coordinates all of the Institutes involved in AIDS research, will play an important role in this effort as well.

Clinical Trials Networks

5. What is a Clinical Trials Network?

Each Clinical Trials Network will consist of the following

- Network Leadership, which comprises
  - Coordinating and Operations Center (CORE) to provide scientific and administrative leadership, central operations and communications
  - Statistical and Data Management Center (SDMC) to provide biostatistical leadership and central data management
  - Network Laboratory to provide the laboratory services necessary to conduct the clinical research
- Clinical Trials Units (CTUs), which comprise
  - An administrative component located at the awardee institution to provide oversight, coordination and administrative support for each clinical research site
  - One or more clinical research sites where qualified professionals conduct clinical research activities

6. What is the Network Leadership and what is its role?

Each Network will be headed by a Principal Investigator (PI), who will be responsible for the scientific leadership and administrative coordination of all Network activities and will oversee operations within the Coordinating and Operations Center (CORE). The Statistical and Data Management Center (SDMC) and Network Laboratory U01 awards may have the same or different PIs than the CORE.

The Leadership of each HIV/AIDS Clinical Trials Network will be responsible for the overall direction and coordination of an HIV/AIDS research plan that responds to one or more of the areas of scientific priority identified by DAIDS. The Network Leadership is also responsible for ensuring that the Network's major structural components are capable of carrying out their respective responsibilities and operate in a well-coordinated fashion. To accomplish these tasks, Network Leadership needs to establish a Network operating structure, including an Executive Committee and Scientific and Resource Committees.

Network Leadership will also be responsible for working collaboratively with other DAIDS- and NIH-sponsored HIV/AIDS research programs, particularly with regard to development of international sites in resource-limited settings; harmonization of laboratory resources and specimen management; common data elements and data entry interfaces; the development, training and support of Community Advisory Boards; and site staff training.

Network Leadership will be required to implement processes and procedures for ongoing evaluation of all Network components, including the Coordinating and Operations Center, Statistical and Data Management Centers, Network Laboratory(s), committees, protocol teams and clinical trial units. A portion of the award for each Network Leadership will be reserved to provide for managerial flexibility and the ability to address unexpected scientific opportunities.

7. What is a Clinical Trials Unit?

A Clinical Trials Unit comprises an administrative component, one or more research sites conducting clinical trials within one or more Clinical Trials Networks, and a community advisory board. CTUs will be solicited through a RFA entitled "Units for HIV/AIDS Clinical Trials Networks," to be issued in early 2005.

Implementation and Evaluation

8. Will the Networks be able to pursue research outside of the six high-priority areas?

No. Funding for this RFA is for applicants who propose a focused research plan in one or more of the six high-priority areas defined by the RFA.

9. How will DAIDS ensure that the Networks are addressing the highest priorities of HIV/AIDS clinical trials research in an efficient, collaborative manner?

A Managing Partners Committee, composed in part of representatives from each Network Leadership, will be established with the primary responsibility of ensuring that a sound inter-network coordination plan is finalized and implemented. In addition, DAIDS will organize periodic external reviews of the scientific plans, priorities and progress of the Networks. Together, the individual Network evaluation plans, the activities of Managing Partners and oversight of the Managing Partners Committee by DAIDS, along with rigorous external review, will help ensure that the issues of inter-network collaboration, redundancy and efficiency are addressed.

10. Does NIAID pursue HIV treatment, prevention and vaccine clinical research exclusively through these Networks?

No. In addition to the multicenter clinical trials research conducted through the Networks, NIAID supports a broad array of solicited and unsolicited investigator-initiated clinical trials, as well as observational and epidemiologic research.

11. Will NIAID continue to support unsolicited, non-network clinical research?

Yes. NIAID must support a diverse portfolio of HIV/AIDS clinical research capabilities to meet its scientific priorities. At present, DAIDS conducts clinical research through seven clinical trials networks and programs, solicited research programs and through non-network, investigator-initiated awards. Solicited research (for clinical trials networks as well as other programs) is funded through awards made in response to specific requests for applications (RFAs) or program announcements (PAs) that are developed by DAIDS in an effort to focus research on specific scientific objectives. Non-network investigator-initiated research is funded through awards made to investigators who submit unsolicited grant applications based on their personal knowledge and awareness of DAIDS' scientific priorities and their own research interests.

While this RFA focuses on the Networks for the conduct of clinical trials, DAIDS will continue to support non-network, investigator-initiated research mechanisms to address specific, high-priority HIV/AIDS clinical research questions. DAIDS currently supports a variety of investigator-initiated trials ranging from single-site studies to large multinational projects, across the spectrum of vaccine, prevention and treatment both in the United States and internationally (especially resource-limited settings), and will continue to do so.

Application and Review Process

12. Who is eligible to apply under the Leadership for HIV/AIDS Clinical Trials Networks RFA?

Eligible organizations include U.S.-based public or private organizations, which can be for-profit or nonprofit in nature, including universities, colleges, hospitals, laboratories, divisions of state and local governments and eligible agencies of the U.S. federal government.

13. What is the timeline for the application process and awards?

The RFA for Leadership for HIV/AIDS Clinical Trials Networks was issued on November 19, 2004. A pre-application meeting will be held to brief potential applicants for the Leadership awards on December 13, 2004. Letters of intent are requested by April 11, 2005. The receipt date for Leadership applications is May 11, 2005. The earliest anticipated award date is March 2006.

14. How will applications for Network Leadership be reviewed?

NIAID will use the standard and rigorous peer review process established by NIH to evaluate applications. Detailed criteria for evaluating each aspect of any application for Network Leadership are delineated in Section V(1) of the RFA. With respect to the merit of the scientific research plan proposed by an applicant, reviewers will assess an application based on the following key questions

- **Significance**—Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services or preventative interventions that drive this field?

- **Approach**—Are the conceptual or clinical framework, design, methods and analyses adequately developed, well integrated, well reasoned and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

- **Innovation**—Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools or technologies for this area?

- **Investigators**—Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

- **Environment**—Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

Reviewers also will assess each applicant's proposed budget, protections for human subjects, and inclusion of women, minorities and children in research. There are several other RFA-specific evaluation criteria, detailed in section V(2)of the RFA. These include three evaluation criteria for the Network Clinical Research Plans, three criteria for the Plans for Cross-Network Collaboration, six criteria for the Network Structure and Leadership Capacity, eight criteria for the Network Policies and Procedures, and eight criteria for the Operations Center capabilities. In addition to scientific merit, final award decisions will be based on DAIDS' scientific priorities and availability of funds.

15. How will the peer review process be organized?

Separate peer review panels will be established to review each scientific priority area proposed in the CORE component and to review the Network Laboratory Structure and Statistical and Data Management Center components. Applications will be evaluated according to the multiple scientific priorities addressed in the proposed research plan, ensuring that only the strongest areas of work will be considered for an award. The evaluation process will help to ensure that each scientific priority area is addressed by the most qualified Network(s). In addition to this first level of peer review, all decisions will be reviewed by the AIDS Subcommittee of the National Advisory Allergy and Infectious Diseases Council.

16. Who will serve on the peer review committees?

The peer review committees will be composed primarily of non-government experts who will assess the merits of each application based on the review criteria included in the RFA. Members will likely include clinical and laboratory investigators working in the United States and abroad, primary care providers, research staff, community representatives, public health experts and individuals with experience working in resource-limited settings.

17. What is the total funding and duration of these awards?

Funding for both the Network Leadership and the Clinical Trials Units is expected to total up to $300 million for the first year, and funding may continue for up to seven years.

It is expected that the Leadership of approximately three to six HIV/AIDS Clinical Trials Networks will be established through this RFA, and that one or more Networks will be established to implement a clinical research plan for each of the six priority research areas.

Role of Community

18. What role will the community have in a network?

Community representatives will continue to be involved in all aspects of the research process, including through a Network Community Advisory Board (CAB). Applicants for the Network Leadership will be asked to demonstrate how they will build community partnerships and incorporate community representatives into the overall management (e.g., governing body) and scientific structure (e.g., scientific committees, protocol teams) of the Network. Establishment of a local Community Advisory Board to work with the Clinical Trials Unit staff and Principal Investigator is also anticipated.

In addition, a new group known as the Community Partners will be established to promote effective representation of, and timely communication among, the many communities, domestically and internationally, working with the Clinical Trials Networks. Responsibilities of the Community Partners will include

- Enhancing intra- and inter-network community input at all levels by participating in and/or providing input to the Managing Partners, External Scientific Review process and directly to the Division of AIDS
- Identifying and developing programs to meet the training and support requirements of local Community Advisory Boards
- Increasing the representation and participation of community representatives from resource-limited settings
- Identifying and addressing challenges to participation in clinical trials, such as economic barriers, cultural beliefs and language issues

Membership for the Community Partners will be drawn from the Network Community Advisory Boards, the Managing Partners and representatives from DAIDS. Additional members may be appointed by the Director of DAIDS, as necessary, to ensure effective regional, national and international representation and for effective communications with other involved NIH Institutes and Centers and Clinical Trials Networks.

Additional Information

19. Are resources available to answer questions related to the RFA and the application process?

The Web site, http://www.niaid.nih.gov/daids/rfa/network06/, contains links to the RFA, useful background material, application instructions and forms and templates for applicants to use in responding to the RFA. The RFA also lists individuals to whom specific questions may be addressed.

Background

20. What is the mission of the DAIDS?

DAIDS was formed in 1986 as part of NIAID, to address the national research needs created by the emergence and spread of the HIV/AIDS epidemic. The Division's mission is to help ensure an end to the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis, natural history and transmission of HIV disease, and supporting research that promotes progress in its detection, treatment and prevention. DAIDS pursues its mission by planning, implementing, managing and evaluating programs in (1) fundamental basic research, (2) discovery and development of therapies for HIV infection and its complications, and (3) discovery and development of vaccines and other prevention strategies.

21. What are the current DAIDS-sponsored HIV/AIDS Clinical Trials Networks?

DAIDS supports clinical research in HIV vaccine, prevention and therapeutic research through the seven research networks listed below (in order of and with date they were first established).

- *The Adult AIDS Clinical Trials Group* (AACTG) (1987) is the largest HIV clinical trials organization in the world, having conducted more than 360 clinical trials that have produced dramatic and sustained improvements in the clinical care, quality of life and survival of people living with HIV/AIDS. (http://aactg.s-3.com/)
- The *Pediatric AIDS Clinical Trials Group* (PACTG) (1993) evaluates treatments for HIV-infected children and adolescents, and develops new approaches to interrupt transmission. PACTG identified treatments that have reduced the rate of MTCT from 25 percent to 1.5 percent in recent years. PACTG is a joint effort of the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute for Child Health and Human Development (NICHD). (http://pactg.s-3.com/)
- *The Terry Beirn Community Programs for Clinical Research on AIDS* (CPCRA) (1993) conducts clinical research through a national network of community-based clinics to identify the most appropriate use of available therapies in diverse populations. (http://www.cpcra.org/)
- *The Acute HIV Infection and Early Disease Research Program* (AIEDRP) (1997) performs innovative, integrated, pathogenesis and clinical research on acute and early HIV infection. (http://www.aiedrp.org/)
- *Evaluation of Subcutaneous Proleukin in a Randomized International Trial* (ESPRIT) (1999) is a large multicenter clinical trial to evaluate effectiveness of IL-2 (interleukin-2) in maintaining immune function in addition to anti-HIV therapy and the impact on HIV disease progression. (http://www.espritstudy.org/). This trial is fully enrolled and is currently following patients in 25 countries.
- *HIV Vaccine Trials Network* (HVTN) (2000)—HVTN has successfully completed more than 50 trials at more than 25 sites in the United States, Africa, Asia, South America and the Caribbean to assess the safety and immunogenicity of multiple vaccine designs and products. (www.hvtn.org)
- *HIV Prevention Trials Network* (HPTN) (2000)—Co-sponsored by the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse, the HPTN focuses on developing and testing non-vaccine prevention interventions. Areas of focus include prevention of MTCT of HIV, microbicides for preventing sexual transmission of HIV, behavioral prevention

interventions, reduction of intravenous drug abuse, control of other sexually transmitted diseases, and antiretroviral therapies that may reduce the spread of HIV from infected people to their partners. (www.hptn.org)

Media inquiries can be directed to the NIAID OCPL media group at 301-402-1663.

NIAID is a component of the National Institutes of Health (NIH), an agency of the U.S. Department of Health and Human Services. NIAID supports basic and applied research to prevent, diagnose and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from potential agents of bioterrorism. NIAID also supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma and allergies.

Press releases, fact sheets and other NIAID-related materials are available on the NIAID Web site at *http://www.niaid.nih.gov*.

Prepared by:
Office of Communications and Public Liaison
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD 20892

U.S. Department of Health and Human Services